- Assessing the PH Assumption Using Time-Dependent Covariates

When time-dependent variables are used to assess the PH assumption for a time-independent variable, the Cox model is extended to contain product (i.e., interaction) terms involving the timeindependent variable being assessed and some function of time. When assessing predictors one-at-a-time, the extended Cox model takes the general form shown here for the predictor *X*.

$$h(t,X) = h_0(t)\exp[\beta X + g(t)]$$

Some choices for *g(t)* :

$$g(t) = t$$

$$g(t) = logt$$

$$g(t) = \begin{cases} 1 & if\ t \geq t_0 \\ 0 & if\ t \leq t_0 \end{cases}$$

Using the above one-at-a-time model, we assess the PH assumption by testing for the significance of the product term.

$$H_0: \delta = 0$$

The test can be carried out using either a Wald statistic or a likelihood ratio statistic. In either case, the test statistic has a chi-square distribution with one degree of freedom under the null hypothesis.

In addition to a one-at-a-time strategy, the extended Cox model can also be used to assess the PH assumption for several predictors simultaneously as well as for a given predictor adjusted for other predictors in the model.

With the above model, we test for the PH assumption simultaneously by assessing the null hypothesis that all the δi coefficients are equal to zero.

$$H_0: \delta_1 = \delta_2 = \cdots = \delta_p = 0$$

This requires a likelihood ratio chi-square statistic with *p* degrees of freedom, where *p* denotes the number of predictors being assessed. The LR statistic computes the difference between the log likelihood statistic—−2 ln *L*—for the PH model and the log likelihood statistic for the extended Cox model.

$$LR = -2\ln L_{PH\ model} - (-2\ln L_{ext.Cox\ model}) \sim X_p^2$$

Under the null hypothesis, the model reduces to the Cox PH model shown here.

$$h(t,X) = h_0(t)\exp\left(\sum_{i=1}^{p} \beta_i X_i\right)$$

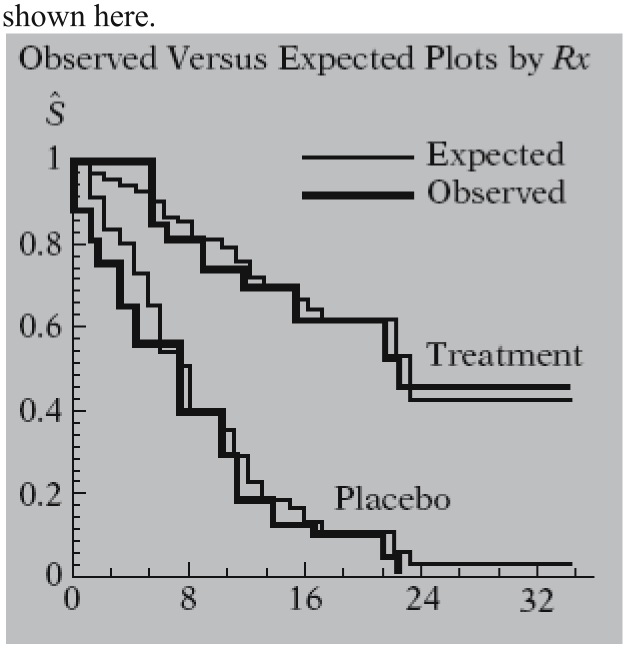
If the above test is found to be significant, then we can conclude that the PH assumption is not satisfied for at least one of the predictors in the model. To determine which predictor(s) do not satisfy the PH assumption, we could proceed by backward elimination of nonsignificant product terms until a final model is attained.

- Observed vs Expected plot

The use of observed versus expected plots to assess the PH assumption is the graphical analog of the goodness-of-fit (GOF) testing approach and is therefore a reasonable alternative to the log–log survival curve approach.
Tthe observed versus expected approach may be carried out using either or both of two strategies :

1. One-at-a-time: uses KM curves to obtain observed plots
2. Adjusting for other variables: uses stratified Cox PH model to obtain observed plots

Here, we describe only the one-at-a-time strategy, which involves using Kaplan-Meier (KM) curves to obtain observed plots. Using the one-at-a-time strategy, we first must stratify our data by categories of the predictor to be assessed. We then obtain observed plots by deriving the KM curves separately for each category.
To obtain "expected" plots, we fit a Cox PH model containing the predictor being assessed. We obtain expected plots by separately substituting the value for each category of the predictor into the formula for the estimated survival curve, thereby obtaining a separate estimated survival curve for each category.
To compare observed with expected plots we then put both sets of plots on the same graph as shown here.



If for each category of the predictor being assessed, the observed and expected plots are “close” to one another, we then can conclude that the PH assumption is satisfied. If, however, one or more categories show quite discrepant observed and expected plots, we conclude that the PH assumption is violated.